Drug-Device Combination Products: A Quality Perspective

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CDER | US FDA

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Disclaimer

This presentation is not intended to convey formal FDA policy

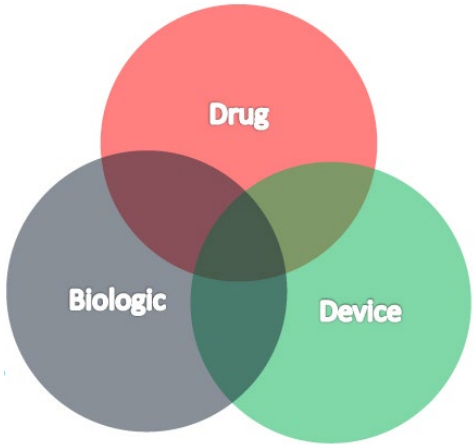
Presentation Outline

- Introduction of Drug Device Combination Products (DDCPs)
- Assessment team structure & process for generic DDCPs
- Drug Product critical quality tests for Parenteral products
- Recommended Performance tests of DDCPs
- Common deficiencies in generic DDCPs
- Case studies

What is a Combination Product ?

A product comprised of two or more regulated components:

- drug/device, biologic/device, drug/biologic or drug/device/biologic per 21 CFR 3.2(e)



Current Good Manufacturing Practice (CGMP) Requirements for Combination Products:

21 CFR Part 4 & 21 CFR 4.4 (b) (2)

- Drug CGMP: 21 CFR parts 210 and 211
- Device: Quality Management System Regulation (QMSR): 21 CFR part 820

CDER as Lead Center

- ***Primary mode of action*** (PMOA) is the single mode of action of a combination product that provides the most important therapeutic action of the combination product (21 CFR 3.2 (m)).

Drug provides the PMOA: CDER is Lead Center

Therapeutic Equivalence-DDCP

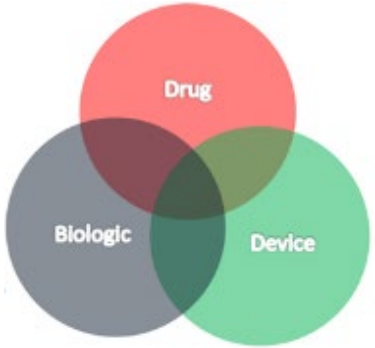
A generic combination product classified as therapeutically equivalent to the RLD can be expected to produce

- the same clinical effect and safety profile as the RLD under the conditions specified in labeling

➢ *confirm that the differences in device and labeling for the proposed generic combination product are acceptable and that the proposed generic combination product can be substituted with RLD*

Types of Combination Products

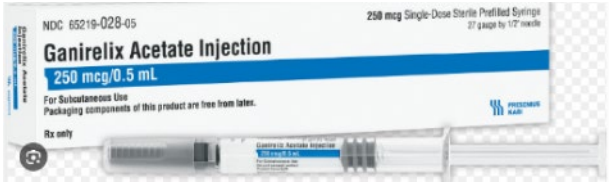
- Per 21 CFR part 3.2(e), combination products include:
  - **Single entity:** physically, chemically, or otherwise combined or mixed
  - **Co-packaged/ Kit**: Two or more separate products packaged together in a single package or as a unit
  - **Cross-labeled**: packaged separately, but labeled for use together as DDCP



Single entity

- Components are physically or chemically combined or mixed and produced as *single entity* (21 CFR 3.2(e)(1)

  - ❖ Prefilled syringe,

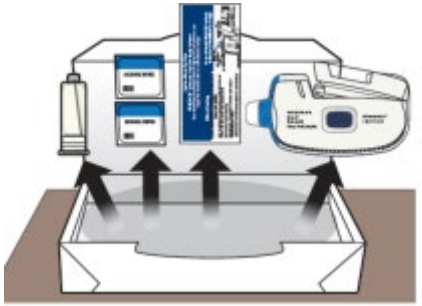


  - ❖ IV bags prefilled with drugs

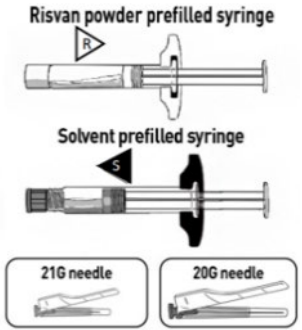
Note: Unfilled IV bags are classified as devices.
See, 21 CFR 880.5025 IV container

Co-packaged/ Kit

- **Co-packaged/ Kit:** Two or more separate products packed together in a single pack or as a unit; 21 CFR 3.2(e)(2)
- Drug in vial + syringe
- Drug in PFS + on-body infusor
- Drug in vial + syringe prefilled with diluent
- First-aid or surgical kit



Furoscix Injection



Risperidone

Cross labeled

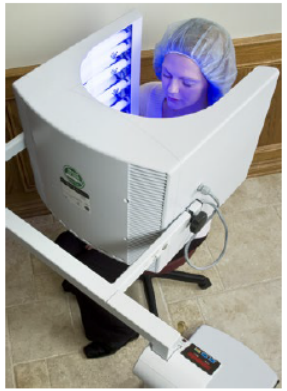
- **Cross-labeled**: packaged separately, but labeled for use together; 21 CFR 3.2 (e)(3) or (e)(4)

➢ Example:

Drug Constituent Part

+

Device Constituent Part



Levulan® Kerastick® (aminolevulinic acid HCl) for Topical Solution, 20% (LEVULAN KERASTICK) plus blue light illumination using the BLU-U® Blue Light Photodynamic Therapy Illuminator (LEVULAN KERASTICK and BLU-U PDT) is indicated for the treatment of minimally to moderately thick actinic keratosis of the face or scalp.

PSG for Complex DDCPs

Device section: Product-specific, unique, device constituent features that affect the product user interface

Contains Nonbinding Recommendations

Draft – Not for Implementation

Draft Guidance on Liraglutide

December 2025

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the Office of Generic Drugs.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

Active Ingredient:	Liraglutide
Dosage Form:	Solution
Route:	Subcutaneous
Strength:	18 mg/3 mL (6 mg/mL)
Recommended Study:	Request for waiver of in vivo bioequivalence study requirements

Non-clinical methods can be used to demonstrate comparable safety and efficacy profiles between a proposed generic peptide (recombinant or synthetically produced) and the reference standard (RS). Unlike synthetic peptides, recombinant peptides may also contain impurities, such as host cell proteins and residual DNA, from the host cell. Therefore, FDA recommends that applicants demonstrate and justify these host cell related impurities are well controlled if the proposed generic peptide product is manufactured using a recombinant process.[5]

Additional information:

Device:

The RLD is presented in a prefilled pen injector. The pen injector is the device constituent part.

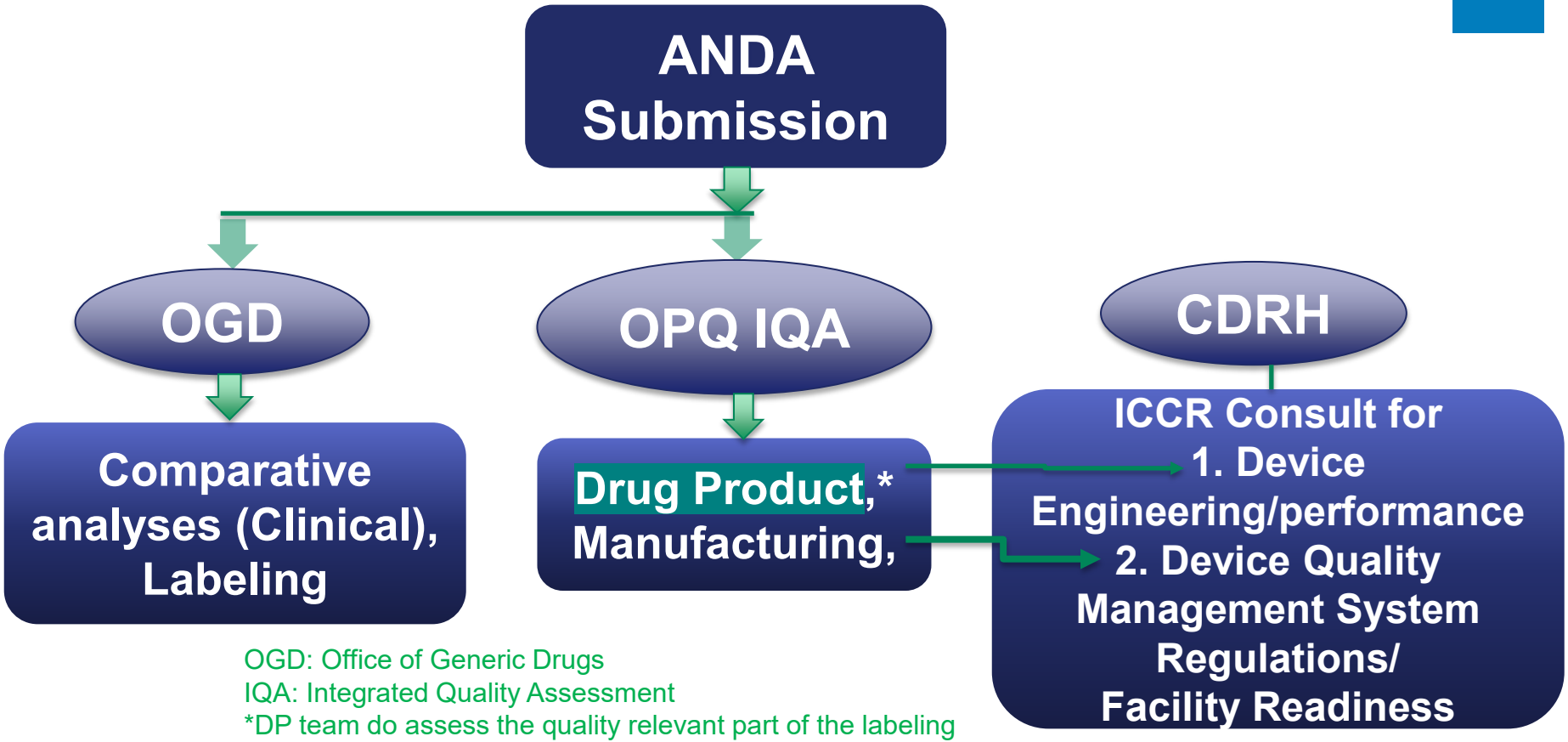
FDA recommends that prospective applicants examine the size and shape, the external critical design attributes, and the external operating principles of the RLD device when designing the test device including:

- Single-patient-use, disposable pen injector with variable-dose format
- Dose selector and dose button
- Needle compatibility

User interface assessment:

An ANDA for this product should include complete comparative analyses so FDA can determine whether any differences in design for the user interface of the proposed generic product, as compared to the RLD, are acceptable and whether the product can be expected to have the same clinical effect and safety profile as the RLD when administered to patients under the conditions specified in the labeling. For additional information, refer to the most recent version of the FDA guidance for industry on *Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA.*[a]

CDER-led DDCP Assessment Teams-ANDAs



OGD: Office of Generic Drugs
IQA: Integrated Quality Assessment
*DP team do assess the quality relevant part of the labeling
ICCR: Inter Center Consult Request

Drug Product Development Stage

- Quality Target Product Profile (QTTP)
- Critical Quality Attributes (CQAs)
- Critical Material Attributes (CMA)
- Risk mitigation strategy
- Comparative physicochemical, in vitro characterization & device performance data of test product with RLD for DDCPs

Drug Product Quality Tests-Injectable solutions

Tests	Reference	Release	Stability
USP general chapter for Parenteral	USP<1>	X	X
Description		X	X
Identification tests		X	
Assay	USP<621>	X	X
Degradation Products	USP<621>	X	X
Container content	USP<697>	X	X
Foreign & Particulate matter	USP<788>, <790>	X	X
Deliverable volume		X	X
Residual Solvents	USP<467>	X	
pH, Osmolality (as applicable)		X	X
Sterility & Bacterial Endotoxin tests	USP<71>, <85>	X	X

Drug Product Quality Tests-Parenteral Suspensions

In addition to the quality tests for Injectables;

Tests	Reference	Release	Stability
Dissolution	USP<711>	X	X
Viscosity (as applicable)	USP<912>		
Uniformity of Dosage units	USP<905>	X	X
Sedimentation volume		X	X
Sedimentation rate		X	X
Redispersibility		X	X
Particle size & size distribution		X	X

General container closure tests: USP chapters: <660>, <661>, <381>, <87>, <88>,<1663>, <1664>

Recommended Performance Tests

Performance tests	Prefilled syringe (Simple PFS)
Break loose force	X
Glide force	X
Dose accuracy/Deliverable volume	X
Cap removal force (for emergency)	*X*
Injectability/syringeability (needle gauge & length)	X

Recommended Performance Tests

Performance tests	Pen-Injector	Auto-injector	On-Body Injector
Dial Torque	X		
Dose accuracy/Delivered volume	X	X	X
Cap removal force	X	X	X
Injection force	X		
Button Activation force		X	X
Extended Needle/canula length		X	X
Injection Time/dose delivery time	X	X	X
Break loose force & Glide force			X
Dose delivery profile (flow rate)			X
Adhesion peel force			X
Audible/visual/tactile feedback	X	X	X

Stability Study Recommendations for DDCPs

At the time of ANDA submission:

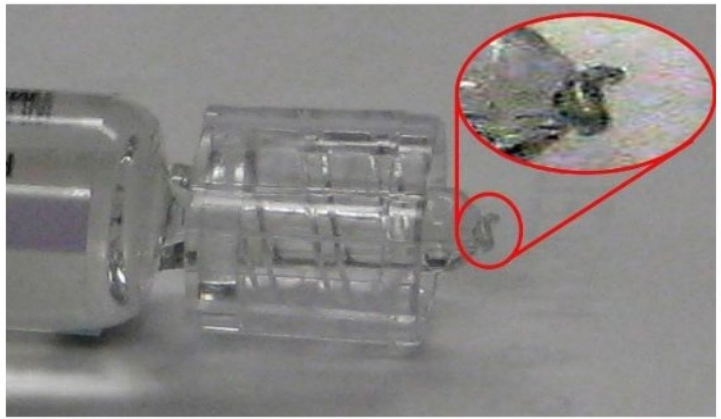
- **Three batches of product, in the proposed container closure system for marketing**
  - For injectors: One batch filled, fully assembled, and fully packaged
  - Two batches, representative number assembled into the device
- Not necessary to use different lots of packaging material
- **Stability orientation:**
  - Primary batches in inverted (or horizontal) position and an upright (or vertical) position
  - For routine stability studies, pick the worst-case orientation

Common Deficiencies in DDCP ANDAs

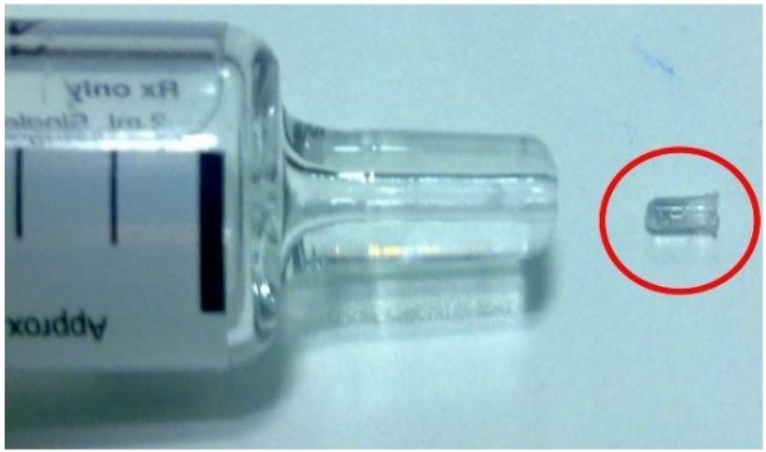
- Delivered dose accuracy and precision
- Air bubble/headspace assessment in PFS
- Break-loose and glide force testing
- Primary container closure failure (on body injectors)
- Adhesion & wearability issues (Adhesive performance problems, biocompatibility concerns)
- Inadequate peel force specification, limited testing conditions
- Unresolved Device Performance Issues
- Failure to Evaluate Temperature Excursion Effects
- Inadequate In-Use Stability
- Extractable & Leachable Assessment

Case Study: Device Incompatibility

- FDA Drug Safety Alert in 2010, 2011
- FDA safety alert issued in 2022 - PFS & Luer activated valve connectors.



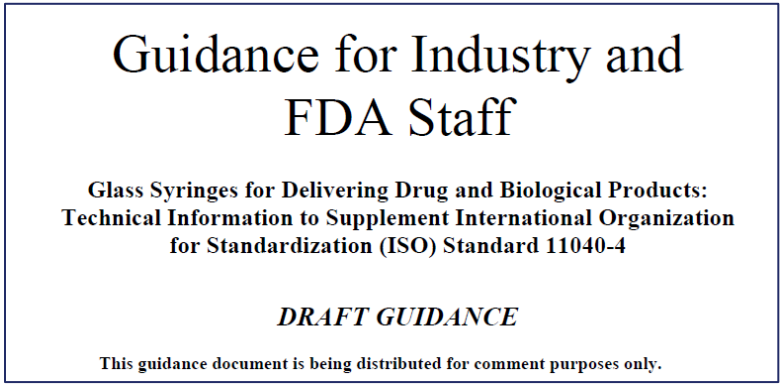
After connecting the glass syringe to the LAV connector, the pin from the connector became clogged in the syringe tip



Pin from LAV connector removed from the syringe tip.

PFS-Luer lock issue

FDA Draft Guidance 2013 for glass syringes



Guidance for Industry and FDA Staff

Glass Syringes for Delivering Drug and Biological Products: Technical Information to Supplement International Organization for Standardization (ISO) Standard 11040-4

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

List of Functional performance of syringe

- **Early interaction** with the Agency
- Request a joint meeting (CDER, CDRH & the applicant)
- Outline your proposed steps to ensure the connectivity of the glass syringe when connected to connecting devices

Case Study - Example 1

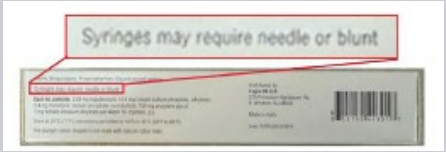
Material	Product A	Product B	RLD
Syringe barrel tubing	Glass 	Glass  	single-dose vial and a SAFT-Jet® vial injector, 27 G. x ½" needle
Luer lock adapter	Glass	Polycarbonate	-
Connectors tested (CDRH consult)	BD Q-style; BD-SmartSite Bionector Arterial connector with an internal pin design (Internal Diameter: **0.043")**	Comparative threshold analysis-low risk No warning in label	No warning in label

For A:

www

CAUTION: The syringe may not be compatible with Luer-activated valve (LAV) connectors that have internal pin designs, such as LAVs with CLAVE design.

Case Study - Example 2

Material	Issue A	Issue B	RLD
ANDA: Syringe barrel tubing-Glass luer lock: Plastic	A protrusion from the tip of the syringe punctured the IV line-medication leak. The luer syringe connector dislodged from the syringe. 	The syringe would not attach and fell to the floor.  'Syringes may require needle or blunt'	For RLD, barrel/luer-lock materials: **plastic**
Label	**Outcome: Caution statement added** **Listed acceptable luer activated connectors.** **Stated incompatibility with LAV connectors such as CLAVE design**	**Outcome: New PFS-glass barrel Hylock.** **The internal bore diameter of the luer is 0.068" .** **No warning**	No compatibility warning

Manufacturer of Clave connectors warning: users should confirm mating luers or syringes have an internal diameter range of **0.062" to 0.110"**.

Summary

- Know your product & the RLD well to avoid delay in approval
- Understand Critical Quality considerations and Device performance expectations for DDCPs
- Communicate early with the Agency

Acknowledgements

- Jin Xu, PhD
- Brock Roughton, PhD
- Pahala Simamora, PhD
- SBIA Organizers

Resources

- Guidance & Regulatory Information | FDA
- https://www.fda.gov/regulatory-information/search-fda-guidance-documents/technical-considerations-pen-jet-and-related-injectors-intended-use-drugs-and-biological-products
- https://www.fda.gov/regulatory-information/search-fda-guidance-documents/glass-syringes-delivering-drug-and-biological-products-technical-information-supplement
- https://www.fda.gov/regulatory-information/search-fda-guidance-documents/container-closure-systems-packaging-human-drugs-and-biologics
- https://www.fda.gov/industry/generic-drug-user-fee-amendments/controlled-correspondence-related-generic-drug-development
- https://www.fda.gov/drugs/guidances-drugs/product-specific-guidances-generic-drug-development
- https://www.fda.gov/regulatory-information/search-fda-guidance-documents/anda-submissions-refuse-receive-standards-rev2

Resources

- https://www.fda.gov/regulatory-information/search-fda-guidance-documents/formal-meetings-between-fda-and-anda-applicants-complex-products-under-gdufa-guidance-industry
- https://www.fda.gov/combination-products/guidance-regulatory-information/acts-rules-and-regulations
- CDER Manual of Policies & Procedures | MAPP: MAPP 5240.10: Classifying Approved New Drug Products and Drug-device Combination Products as Complex Products for Generic Drug Development Purposes
- https://www.fda.gov/combination-products/about-combination-products/combination-product-definition-combination-product-types
- https://www.fda.gov/combination-products/about-combination-products/frequently-asked-questions-about-combination-products
- https://www.complexgenerics.org/education-training/ddcp-101-identifying-developing-and-evaluating-generic-drug-device-combination-products-ddcp/
- https://www.complexgenerics.org/education-training/drug-device-combination-products-updates-and-challenges-with-demonstrating-generic-substitutability/